DETAILED ACTION

Receipt is acknowledged of an amendment, filed 9/22/2004, in which claim 28 was amended. Currently, claims 1-113 are pending.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 11/27/2007 is acknowledged. Applicant's election without traverse of species (A) detection of nucleic acid (claim 13), and (B) all of the genes in Table II (claim 9) in the reply filed on 11/27/2007 is acknowledged.

Claims 36-113 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/27/2007.

Claims 5-8, 10-12, 16, 17 and 22-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/27/2007. Applicant indicated that claims 1-4, 9, 13-21, 26-29 and 33-35 were readable upon the elected species. However, claims 16 and 17 are specifically drawn to genes in Table IV, and claims 26-29 & 33-35 are drawn to the combination of genes that is each of the genes in Tables I, II, III, IV and V. Thus, claims 16, 17, 26-29 and 33-35 are not readable upon the elected combination of genes, which is all of the genes in Table II.

An examination on the merits of claims 1-4, 9, 13-15 and 18-21 follows.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/365,800, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The specification of Application No. 60/365,800 does not describe the genes that show a substantial or significant difference in expression between a subject with multiple sclerosis and a normal, healthy individual. The specification of the 60/365,800 application describes genes that are differentially expressed between subjects with relapse of multiple sclerosis and remission of multiple sclerosis. The specification of the 60/365,800 application does not describe the genes of instant Tables I or II, for example. Thus, the specification does not provide adequate support or enablement for the claimed method of diagnosing a subject with multiple sclerosis, the method comprising determining a level of expression of at least one gene from Tables I-V, wherein said level of expression is compared to

a normal level of expression, especially for the elected combination of genes, which is all the genes listed in Table II.

Claims 1-4, 9, 13-15 and 18-21 have an effective filing date of 3/13/2003, which is the filing date of PCT/IL03/00208.

Information Disclosure Statement

Receipt of information disclosure statements, filed on 8/10/2006 and 10/18/2006, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The citizenship of Naftali Kaminski was altered. This change was not initialed or dated.

Specification

The disclosure is objected to because of the following informalities:

(i) The specification refers to Table V as containing markers that are distinct between disease-related and non-disease related T-cell myelin reactivity (i.e., differential gene expression in MOG-reactive T-cells MS vs. Healthy). See page 24, lines 22; page 25, line 5; page 47, line 5; and page 48, line 5. These genes are presented in Table IV and not Table V (see page 96).

Table V contains genes described as specific for "probable" MS (e.g., page 45, lines 11-12; page 97).

(ii) In the brief description of the drawings, the specification refers to colors that cannot be seen in the black and white drawings. For example, Figures 1A-B, 2A-B and 4 refer to red, green, blue and yellow portions of the drawings.

Appropriate correction is required.

It is noted that color photographs and color drawings are acceptable only for examination purposes if a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use color photographs as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if all conditions for accepting color drawings have been satisfied.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 28, line 18; page 30, line 10; and page 31, line 22.

The attempt to incorporate subject matter into this application by reference GenBank Accession numbers is ineffective because the specification attempts to incorporate gene sequences identified as entries in an electronic database (page 106, lines 9-14). The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See 37 CFR 1.57(d) and MPEP § 608.01(p), paragraph I regarding incorporation by reference.

The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

The use of the trademarks GENECHIP (page 15, line 14; page 18, line 18; page 29, line 15; page 29, line 28; page 37, line 9; page 37, line 24), and GENBANK (page 20, line 12 to page 21, line 4; page 106, line 10) has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 9, 13-15 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to a method of diagnosing a subject with multiple sclerosis. The generic claim is drawn to step of determining a level of expression of at least one gene selected from the group consisting of the genes listed in Table I-V in a sample obtained from the subject, wherein a substantial difference between said level of expression of said gene in said sample obtained from said subject and a normal expression level of said gene is

an indication that the subject is afflicted with multiple sclerosis. The elected species of genes is all of the genes listed in Table II of the specification. Claim 2 requires the normal expression level of the genes to be determined by measuring the level of expression in at least one control sample obtained from at least one healthy individual. Claim 3 limits the sample to peripheral blood mononuclear cells. Claim 4 limits the substantial difference to a difference statistically significant at a confidence level of p=0.5 as determined by at least one test selected from the group consisting of a t-test, a TNoM and an INFO score. Claims 13 and 14 limit the detection step to the detection of a transcribed polynucleotide and mRNA, respectively. The nature of the invention is complex in that the level of gene expression must reliably classify a subject as having multiple sclerosis or as not having multiple sclerosis.

Breadth of the claims: The claims are broadly drawn to the diagnosis of any subject, human or otherwise. The claims encompass the use of any sample in the claimed assay. Even for the use of peripheral blood mononuclear cells (PBMCs), the specification envisions obtaining these cells from blood or any other tissue that may have PBMCs as an infiltrate (e.g., paragraph bridging pages 19-20). The generic claim is drawn to the determination of at least one gene selected from the group of genes listed in Tables I-V. Thus, the claims are broadly drawn to measuring the expression level of one or more than 1200 genes. The claims are broadly drawn to the diagnosis of multiple sclerosis based upon a "substantial difference" in gene expression between the subject and a "normal expression level." The claims encompass embodiments where the difference is relative to a single control individual and where the difference may appear substantial but is not statistically significant. The claims encompass the use of any control individual and do not require a group of healthy individuals that are sex- and age-

matched to the subject. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches the identification of a set of genes that are differentially expressed between humans with multiple sclerosis (MS) and a group of healthy sex- and age-matched controls, where the difference in expression is statistically significant (e.g., Example I). A minimal set of genes that can be used to reliably classify a subject as having or not having MS is disclosed in Table II. A larger set of genes comprising all of the genes recited in Table II is disclosed in Table I. The specification teaches that these differences in gene expression are observed in mRNA isolated from PBMCs obtained from the blood of subjects and controls (e.g., pages 36-37).

The elected species is all of the genes of Table II. The claims encompass the measurement of expression level of all of the genes of Table II by detecting the level of mRNA expression. Thus, the sequences of the genes are critical or essential to the practice of the invention. However, some genes are referred to by only a GenBank Accession No., and the specification does not contain the sequences of the GenBank Accession numbers. The specification attempts to incorporate this essential subject matter into this application by reference to the GenBank Accession numbers but is ineffective (page 106, lines 9-14). The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See 37 CFR 1.57(d) and MPEP § 608.01(p), paragraph I regarding incorporation by reference. The nucleic acid sequences of the GenBank Accession Nos. disclosed in Table II are critical or essential to the practice of the invention, but not included in the claim(s) are not

enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The GenBank Accession numbers refer to entries in an electronic database which is subject to change over time (see Exhibit A). "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. In the instant case, the claims are, in effect, incorporating the sequence of the GenBank Accession numbers by reference to the entries in the electronic database. "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." See MPEP 608.01(p). Accordingly, the reference to the GenBank Accession numbers does not provide the features that are critical or essential to the practice of the claimed invention. For those genes that were well known in the art at the time the invention was made and where the gene name is sufficient to identify the specific sequence of the transcript and protein which is to be used in the step of "determining a level of gene expression," the nucleic acid and amino acid sequences need not be explicitly disclosed in the specification.

The specification does not teach the use of the genes of Tables III-V to diagnose a subject with MS. The genes of Table III are disclosed as being differentially expressed between relapsing MS and remitting MS (e.g., Example II). The genes of Table IV are disclosed as being differentially expressed in cultured T-cell lines of individuals with and without multiple sclerosis; however, the specification does not teach the ability of these genes to reliably classify an individual as having or not having multiple sclerosis. The genes of Table V are disclosed as

being differentially expressed in individuals with "probable" MS and healthy individuals. The individuals defined as "probable" MS do not have a clinical diagnosis of MS and are characterized by diverse neurological symptoms (e.g., paragraph bridging pages 44-45).

Predictability and state of the art: The art teaches that gene expression analysis is commonly used for three different purposes: (1) as a screening tool to identify individual genes of interest that might contribute to an important biological function, (2) to obtain insight into an important biological function, and (3) as a classification tool to sort cases into clinically important categories (Pusztai and Hess, Annals of Oncology, Vol. 15, pages 1731-1737, 2004; e.g., paragraph bridging pages 1732-1733). The prior art reveals that differences in gene expression observed between two groups are do not necessarily provide markers that can be used to reliably classify a subject. Golub et al (Science, Bol. 286, pages 531-537, October 1999) teach the use of a two-step procedure to test the validity of gene expression levels as predictors: step 1 involves cross-validation of the predictors on the initial data set, where one withholds a samples, builds a predictor based only on the remaining samples and predicts the class of the withheld sample; step 2 involves the repetition of assessing the clinical accuracy of the predictor set on an independent set of samples (e.g., page 532, right column). Although Golub et al could detect gene expression differences between chemotherapy responders and non-responders, those differences could not be use to predictably classify individuals (e.g., page 533, paragraph bridging left and middle columns). In the instant case, the specification uses gene expression analysis to classify an individual as having or not having MS, where the smallest set of genes disclosed as having this discriminating capability is the set of genes listed in Table II. However,

the claims are drawn to using gene expression analysis of a single gene or genes not disclosed as being differentially expressed between MS and healthy individuals (e.g., the genes of Table III).

Further, Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (e.g., paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (e.g., paragraph [0156]). Pusztai and Hess teach that larger samples sizes may be needed to validate classification tests, and the number of samples will vary depending upon the acceptable error rates, level of inter-patient variability, the size of the difference in mean expression values, and the prevalence of the phenotype among the group being tested (e.g., page 1734, paragraph bridging columns; Table 1). The present specification does not teach the validation of the diagnostic test with a set of genes smaller than all of the genes listed in Table II. It would unpredictable to use less than all the genes in Table II to make the diagnosis required by the claimed invention. Furthermore, the specification does not teach the diagnosis of an individual where only one individual is used as a normal, healthy control. The specification teaches the use of a group of age- and sex-matched control subjects. It would be unpredictable to carry out the claimed invention with a single healthy control subject, due to the differences in gene expression that may occur between two individuals by chance and which may not accurately diagnose the test subject.

The prior art teaches that common patterns of gene expression are found in the PBMCs of subjects with clinically distinct autoimmune diseases, including rheumatoid arthritis (RA), MS, type I diabetes and systemic lupus erythematosus (SLE) (Maas et al. The Journal of Immunology, Vol. 169, pages 5-9, July 2002; e.g., page 5, right column, 1st full paragraph; paragraph bridging pages 6-7; page 7, paragraph bridging columns; Figure 2). The post filing art confirms that autoimmune diseases share a common autoimmunity specific signature and demonstrates a common signature for MS and SLE (Mandel et al. Clinical and Experimental Immunology, Vol. 138, pages 164-170, October 2004; e.g., paragraph bridging pages 165 & 167 and Figure 1). The specification asserts that VEGF is differentially expressed in MS, as compared to healthy individuals (e.g., paragraph bridging pages 20-21; page 42, line 15; Table I, row 4; Table II on page 75). However, VEGF is not specific to MS, because Mandel et al teach that VEGF is a gene that contributes to the common autoimmunity signature for MS and SLE (e.g., Table I). Thus, it would be unpredictable to practice the claimed invention with less than all the genes in Table II.

Amount of experimentation necessary: Given the lack of guidance in the specification and prior art with regard to the diagnosis of MS by determining the level of expression of "at least one gene" of Tables I-V of the present specification, the quantity of experimentation in this area is very large. Because the specification identifies the set of genes disclosed in Table II as the smallest set of genes predictive of MS, it would be unpredictable to use a smaller set of genes without performing rigorous statistical analysis. One would be required to perform additional tests to identify subsets of the disclosed genes that are capable of providing a reliable diagnostic test for MS. Furthermore, one would be required to perform a large amount of experimentation

to determine if the test could be preformed with a single control subject and without the use of statistical tests such as a t-test, TNoM or an INFO score. In other words, one would be required to perform additional experiments to use the claimed method as a qualitative assay of substantial gene expression changes to diagnose a subject with MS. Moreover, one would be required to identify tissues other than PBMC isolated from blood for which the level of expression of any combination of genes, including all the genes in Table II, would be diagnostic for MS in humans and other animals, as encompassed by the claims.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1-4, 9, 13-15 and 18-21 are not considered to be enabled by the instant specification.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Daniel M Sullivan/
Primary Examiner, Art Unit 1636

GI State Page 1 of 1

Exhibit A

NCBI

Sequence Revision History

Find (Accessions, GI numbers or Fasta style SeqIds) ab002344

About Entrez

Show difference between I and II as GenBank/GenPept

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Revision history for AB002344

GI	Version	Update Date	Status	I	II
20521008	2	Dec 26 2006 11:35 PM	Live		
20521008	2	Aug 2 2006 5:47 PM	Dead		
20521008	2	May 9 2002 11:31 PM	Dead		
2280479	1	Oct 6 2001 11:11 PM	Dead		
2280479	1	Mar 16 1999 10:34 PM	Dead		
2280479	1	Jul 25 1997 1:49 AM	Dead		
2224632	0	Jun 27 1997 2:16 AM	Dead		

Accession AB002344 was first seen at NCBI on Jun 27 1997 2:16 AM

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